Flare Phenomenon Following Gefitinib Treatment of Lung Adenocarcinoma with Bone Metastasis

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The skeleton is the most common site for distant metastasis in patients with cancer. To detect bone metastasis and evaluate the efficacy of treatment, we usually use bone scintigraphy and check serum alkaline phosphatase (ALP). However, such evaluation is sometimes difficult due to flare phenomenon. A 61-year-old male was referred to our department with a suspected diagnosis of lung cancer. Following thorough examinations, he was diagnosed with primary lung cancer (adenocarcinoma, Stage IV) and found to have a mutation in the epidermal growth factor receptor gene at exon 21 (L858R). After initiating treatment with oral gefitinib, ALP increased and peaked at 3,592 U/L by 3 weeks and decreased thereafter. At 4 weeks following treatment initiation, bone scintigraphy revealed a marked increase in abnormal accumulation of 99mTc-polyphosphate, but the primary tumor and metastases in regions other than the bone were reduced. At 9 weeks after treatment initiation, abnormal accumulations was improved in bone scintigraphy, and computed tomography revealed osteoblastic changes consistent with the accumulated lesion observed by bone scintigraphy. After initiating cancer treatment for bone metastasis, it is not uncommon to observe transient asynchronous accumulation in bone scintigraphy or transient increases in ALP in patients who ultimately respond to the treatment. These changes are called flare phenomenon, and documented in patients with prostate cancer or breast cancer receiving treatment. When determining the efficacy of treatments that target carcinomas with bone metastases, it is important to note that flare phenomenon is often indistinguishable from disease progression indicators.

Keywords: bone metastasis; bone scintigraphy; flare phenomenon; gefitinib; lung cancer

Bone metastases are a major clinical problem in lung cancer. Assessment of objective response to treatment in bone is estimated by bone scintigraphy, alkaline phosphatase (ALP), urinary calcium and carcinoembryonic antigen (CEA). After initiating cancer treatment, it is not uncommon to observe transient asynchronous accumulation in bone scintigraphy or transient increases in ALP in patients who ultimately respond to the treatment. These changes are called ‘flare phenomenon’ and were first reported by Greenberg et al. (1972). Flare phenomenon has been reported for prostate cancer and breast cancer, as well as gastroenterological and lung cancers (Killian et al. 1981; Cosolo et al. 1988; Vogel et al. 1995; Amaroso et al. 2007). Unfortunately, the clinical significance and mechanisms underlying the flare phenomenon remain poorly understood.

Here we describe our experience with a patient who presented with flare phenomenon after initiating gefitinib treatment for lung cancer. Incidentally, we observed osteoblastic changes over time concurrent with bone metastases.

Clinical Report

Patient: 61-year-old male.
Primary complaints: Pain on the left side of his face, weight loss, general malaise.
Medical history: Lumbar disk hernia at age 33 (treated with surgery).
Lifestyle: Smoking history of 40 cigarettes/day for 41 years (20-61 years of age), no history of drinking alcohol.
Present history: The patient complained of pain in the left side of his face in July 2010. A local doctor examined and treated him for trigeminal neuralgia, but symptoms did not diminish. Following this, he lost approximately 13 kg of body weight, and was hospitalized in the Internal Medicine Department at a local hospital in November 2010. Chest x-ray and chest CT revealed a tumor in the right inferior lobe, and he was referred to our department with a sus-
expected diagnosis of lung cancer.

Symptoms at hospitalization: Height 172.4 cm, weight 44.5 kg, temperature 37.5°C, blood pressure 102/67 mmHg, pulse 97 bpm, palpebral conjunctiva indicative of anemia but no jaundice, palpable lymph nodes on the left side of his neck, slightly weaker breathing sounds on the inferior right side of the lungs, normal heart rhythm with no murmur, no abnormal findings in the abdomen, left eyelid ptosis and some paralysis of the left corner of the mouth, cacosgeusia, ability to wrinkle forehead.

Findings upon hospitalization (Table 1): Hematological and biochemical tests showed increased white blood cells (12,900/µl), markedly increased CEA (2,370 ng/ml), ALP of 408 U/L, and a normal corrected Ca level of 9.9 mg/dL. Infectious disease tests confirmed untreated chronic hepatitis B.

Chest x-ray (Fig. 1): An infiltrative shadow was confirmed in the mid- to lower right lung field.

Chest CT (Fig. 1): Emphysematous changes were confirmed in both lungs, and an irregularly shaped tumor mea-
suring 6.5 × 5 cm was identified on the right inferior lobe. Enlargement of tracheal bifurcation and right hilar lymph nodes was also confirmed. Many tumors were visualized on the periphery of the left scapula and subcutaneously on the backside. Several tumors were also visualized in the caudal portion of the pancreatic body and the left adrenal gland.

Bone scintigraphy (Fig. 2): Multiple abnormal accumulations indicative of metastases to the spine, pelvic bone, costal bone, and bones in both upper arms and femurs were noted.

Head MRI: Multiple nodal cells were visualized in both cerebral hemispheres.

Marked emaciation was confirmed on admission, and the patient was given a low performance status (PS) of 4. Sputum cytodiagnosis and left back tumor aspiration cytology exam confirmed Class V adenocarcinoma, and PCR revealed a missense mutation in the epidermal growth factor receptor gene at exon 21 (L858R). Based on the above, the patient was diagnosed with primary lung cancer (adenocarcinoma, cT 2b N 2 M 1b , Stage IV). We noted a decreased PS, but began gefitinib treatment following consultation with the patient and his family.

ALP at hospitalization was within the normal range, but after 1, 2, and 3 weeks of oral administration, these values increased markedly to 1,618 U/L, 2,742 U/L, and 3,592 U/L, respectively. At 3 weeks post-administration, given that the ALP cutoffs were 12% for ALP₁ and 88% for ALP₂, and because no substantial abnormalities were confirmed for transaminase or γ-glutamyl transpeptidase, the majority of the ALP was thought to originate from bones. PS noticeably improved after gefitinib, and the patient was able to walk independently with a walker or use a wheelchair for outings. Chest x-ray showed reduced tumor size, and palpation also revealed a reduction in size of the subcutaneous tumor. CEA levels also became lower. However, at 4 weeks after initiating oral gefitinib, bone scintigraphy during a full body examination revealed marked increases in abnormal accumulations of ⁹⁹ᵐTc-polyphosphate; we suspected a worsening of bone metastases. Yet, given the size reductions of the primary tumor and other metastases by CT and increased osteoblastic activity at the site of bone metastases, we suspected a flare phenomenon and continued gefitinib treatment. At 3 weeks of oral gefitinib, ALP peaked and decreased thereafter. The bone scintigraphy taken after 8 weeks of gefitinib confirmed fewer abnormal accumulations. Finally, CT showed a reduction in size of the primary tumor, and we confirmed an increase in osteoblastic changes that coincided with bone metastases (Figs. 3 and 4).

Discussion

Treatment efficacy for cancers involving bone metastases is determined with bone scintigraphy and ALP, in addition to CT and tumor markers. However, there can be discrepancies among different modalities. For example, while bone scintigraphy and ALP values may indicate that the patient’s condition is getting worse, other tests may indicate improvement. Such phenomena are called scintigraphic or ALP flares, and are collectively reported as flare phenomena.

In the normal bone tissue, two main cell types are responsible for the remodelling process. Osteoclasts resorb bone tissue, while osteoblasts replace bone tissue. Likewise, bone metastatic tumor tissues contain both osteoblasts and osteoclasts, and their interaction can make tumors tend to be osteoblastic or osteolytic. Metastatic bone lesions can be classified as osteolytic (bone lysing), osteoblastic (bone forming), and biphenotypic types based on histology. For lung cancer, 20% of non-small cell lung carcinomas and 30-40% of small cell lung carcinomas are complicated by bone metastases (Schumacher et al. 2001; Toloza et al. 2003). The majority of these appear to be osteolytic by imaging, but some are biphenotypic and, in rare cases, osteoblastic (Koizumi 2004).

Bone scintigraphy uses bisphosphonate labeled with ⁹⁹ᵐTc, which is rapidly distributed to bone tissue throughout the body following injection, accumulating as hydroxyapatite created during bone formation. As such, a high level of accumulation is evident during osteoblastic metastases, in which bone formation occurs rapidly. For osteolytic metastases in lung cancer, bone scintigraphy is thought to be applicable for diagnosis only during the reparative process in regions of bone resorption due to metastasis.

Since the first report of bone scintigraphic flare phenomenon in 1972 (Greenberg et al. 1972), other similar
reports have emerged from Europe and the United States (Killian et al. 1981; Pollen et al. 1984). Osteoblastic metastatic tumors in prostate and breast cancer are the most common tumor types, and flare phenomena in lung cancer have been reported on 7 occasions (Cosolo et al. 1988; Lemieux et al. 2002; Arai and Kojima 2007; Chao et al. 2009; Krupitskaya et al. 2009; Lind et al. 2010). Given that bone scintigraphic accumulation increases under conditions of markedly increased bone formation, treatment is thought to cause tumor breakdown in areas afflicted with the metastasis, leading to osteoblastic changes during treatment. In our patient, CT confirmed osteoblastic changes over time in areas where bone scintigraphic accumulation had also increased, indicating a strong association between the flare phenomenon and osteoblastic changes accompanying the treatment of bone metastatic tumors.

ALP resides in the osteoblast cell membrane, and serves as a marker that enters the bloodstream during bone formation. There is currently no clear definition of ALP flare phenomenon, and depending on the report, the frequency and amount of increase varies widely. From previous reports, we know that ALP values follow a pattern consistent with that of bone scintigraphy (Coleman et al. 1988; Arai and Kojima 2007); the present patient also showed fluctuations in ALP values consistent with that observed with bone scintigraphy. This supports the hypothesis that treatment can lead to osteoblastic changes in bone metastases.
Of all available reports on flare phenomena in lung cancer (Table 2), the present study is the first to document osteoblastic changes in CT coinciding with bone scintigraphic flare phenomenon. Other than the present study, only one has reported ALP flare phenomenon in lung cancer, underscoring its rarity (Arai and Kojima 2007). Although the frequency of flare phenomenon in lung cancer is unknown, treatments involving the use of molecular target drugs seem to yield more reports of these phenomena compared to those involving standard cytotoxic chemotherapies. Some studies about bone metastasis of breast cancer have associated flare phenomena with favorable prognoses (Colemaan et al. 1988; Koizumi et al. 1999), and the same has been suggested for lung cancer (Pluquet et al. 2010).

As flare phenomenon represents a transient worsening of patient condition, it is difficult to differentiate between this and an actual worsening in disease activity within a short period. In addition, while rare in lung cancer, if bone metastases present as osteoblastic metastases, the differentiation is complicated even further. Diagnosis of flare phenomenon should consider other scientific findings and test results, and judgments should be based on a broad range of such tests. In particular, if worsening is indicated by bone scintigraphy or ALP findings and is inconsistent with clinical findings, CT should be performed to identify osteoblastic changes in the bone metastasis, and the likelihood of flare phenomenon should be scrutinized.

Conflict of Interest
The authors have no conflict of interest.

References
Schumacher, T., Brink, I., Mix, M., Reinhardt, M., Herget, G., Digel, W., Henke, M., Moser, E. & Nitzsche, E. (2001) FDG-PET imaging for the staging and follow-up of small cell

Table 2: Patients with flare phenomena in lung cancer.

<table>
<thead>
<tr>
<th>Author</th>
<th>Number of patients</th>
<th>Cell type</th>
<th>Treatment</th>
<th>Onset after treatment</th>
<th>Examination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cosolo W et al.</td>
<td>2</td>
<td>SCLC</td>
<td>Cytotoxic chemotherapy</td>
<td>3 months</td>
<td>Bone scintigraphy</td>
</tr>
<tr>
<td>Lemieux J et al.</td>
<td>2</td>
<td>NSCLC</td>
<td>Cytotoxic chemotherapy</td>
<td>6.3 and 13 weeks</td>
<td>Bone scintigraphy</td>
</tr>
<tr>
<td>Arai Y et al.</td>
<td>1</td>
<td>Adenocarcinoma</td>
<td>Gefitinib</td>
<td>3 weeks</td>
<td>ALP</td>
</tr>
<tr>
<td>Chao HS et al.</td>
<td>7</td>
<td>NSCLC (5 adenocarcinoma)</td>
<td>Gefitinib</td>
<td>29-77 days (median: 34 days)</td>
<td>Bone scintigraphy</td>
</tr>
<tr>
<td>Krupitskaya Y et al.</td>
<td>4</td>
<td>Adenocarcinoma</td>
<td>Bevacizumab and cytotoxic chemotherapy</td>
<td>6-9 weeks</td>
<td>F18-FDG PET</td>
</tr>
<tr>
<td>Lind JS et al.</td>
<td>3</td>
<td>Adenocarcinoma</td>
<td>Erlotinib</td>
<td>6 weeks - 3 months</td>
<td>CT</td>
</tr>
<tr>
<td>Present patient</td>
<td>1</td>
<td>Adenocarcinoma</td>
<td>Gefitinib</td>
<td>4 weeks</td>
<td>Bone scintigraphy, ALP</td>
</tr>
</tbody>
</table>

Flare phenomena in lung cancer have been reported on 7 occasions.